Lysophosphatidic acid protects human mesenchymal stromal cells from differentiation-dependent vulnerability to apoptosis.

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Public Summary:
The survival of transplanted cells and their resulting efficacy in cell-based therapies is markedly impaired due to serum deprivation and hypoxia (SD/H) resulting from poor vascularization within tissue defects. Lysophosphatidic acid (LPA) is a platelet-derived growth factor with pleiotropic effects on many cell types. Mesenchymal stromal cells (MSC) exhibit unique secretory and stimulatory characteristics depending on their differentiation state. In light of the potential of MSC in cell-based therapies, we examined the ability of LPA to abrogate SD/H-induced apoptosis in human MSC at increasing stages of osteogenic differentiation in vitro and assessed MSC survival in vivo. Undifferentiated MSC were rescued from SD/H-induced apoptosis by treatment with both 25 and 100 μM LPA. However, MSC conditioned with osteogenic supplements responded to 25 μM LPA, and cells conditioned with dexamethasone-containing osteogenic media required 100 μM LPA. This rescue was mediated through LPA1 in all cases. The addition of 25 μM LPA enhanced vascular endothelial growth factor (VEGF) secretion by MSC in all conditions, but VEGF availability was not responsible for protection against apoptosis. We also showed that codelivery of 25 μM LPA with MSC in alginate hydrogels significantly improved the persistence of undifferentiated MSC in vivo over 4 weeks as measured by bioluminescence imaging. Osteogenic differentiation alone was protective of SD/H-induced apoptosis in vitro, and the synergistic delivery of LPA did not enhance persistence of osteogenically induced MSC in vivo. These data demonstrate that the capacity of LPA to inhibit SD/H-induced apoptosis in MSC is dependent on both the differentiation state and dosage. This information will be valuable for optimizing osteogenic conditioning regimens for MSC before in vivo implementation.

Scientific Abstract:
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